



4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2010-P-0176]

SEDASYS Computer-Assisted Personalized Sedation System; Ethicon Endo-Surgery, Incorporated's Petition for Review of the Food and Drug Administration's Denial of Premarket Approval; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The topic to be discussed is the Center for Device and Radiological Health's (CDRH's) denial of a premarket approval application (PMA) for the SEDASYS computer-assisted personalized sedation system (SEDASYS) submitted by Ethicon Endo-Surgery Inc. (EES)--the sponsor for SEDASYS. The meeting will be open to the public.

Name of Committee: Medical Devices Dispute Resolution Panel of the Medical Devices Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the Agency on scientific disputes between CDRH and sponsors, applicants, and manufacturers

Date and Time: The meeting will be held on December 14, 2011, from 8 a.m. to 6 p.m.

Location: The meeting will be held at the Hilton Washington, DC/North, Salons A, B, C, and D of the Ballroom, 620 Perry Pkwy., Gaithersburg, MD.

Contact Person: Nancy Braier, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, rm. 5454, Silver Spring, MD

20993, 301-796-5676, FAX: 301-847-8510, email: nancy.braier@fda.hhs.gov, or FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), and follow the prompts to the desired center or product area. Please call the Information Line for up-to-date information on this meeting. A notice in the Federal Register about last minute modifications that affect a previously announced advisory committee meeting cannot always be published quickly enough to provide timely notice. Therefore, you should always check the Agency's Web site and call the appropriate advisory committee hot line/phone line to learn about possible modifications before coming to the meeting..

Registration and Presentations: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions from persons other than EES and CDRH may be made to the docket on or before December 7, 2011. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm 1061, Rockville, MD, 20852. It is only necessary to send one set of comments. It is no longer necessary to send two copies of mailed comments. Identify all written and electronic comments and submissions with the docket number found in brackets in the heading of this document. All written and electronic comments and submissions will be considered to be publicly disclosable.

Oral presentations from persons other than EES and CDRH will be scheduled between approximately 8:15 to 8:45 a.m., and 2:15 to 2:45 p.m. on December 14, 2011. If you wish to make an oral presentation during the meeting, you should register on or before November 30, 2011. Send registration information (including name, title, firm name, address, telephone, and FAX number), and requests to make oral presentations to Nancy Braier (see Contact Person).

You should provide the docket number appearing in the heading of this notice. You also should submit a brief summary of the presentation, including the discussion topic(s) that will be addressed and the approximate time requested for your presentation. The amount of time to be allotted to each presenter may be limited to provide opportunities to as many persons wishing to present as possible. If the number of registrants requesting to speak is greater than can be reasonably accommodated during the scheduled open public hearing session, FDA may conduct a lottery to determine the speakers for that session. We encourage individuals and organizations with common interests to consolidate or coordinate their presentations to allow adequate time for each request for presentation. Nancy Braier will notify interested persons regarding their request to speak by December 5, 2011. On the day of the meeting scheduled open public speakers should identify themselves at the registration desk.

After the scheduled speakers have spoken, the Chair of the advisory committee may ask them to remain if the advisory committee wishes to question them further. The Chair may recognize unscheduled speakers should time allow.

I. Background

FDA is announcing that, in accordance with section 515(g)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360e(g)(2)), a public advisory committee will review CDRH's denial of a PMA for the SEDASYS Computer-Assisted Personalized Sedation System submitted by EES--the sponsor for SEDASYS.

On March 25, 2008, EES submitted a PMA (PMA P080009) for SEDASYS. SEDASYS is an integrated patient monitoring and drug delivery system. The device's proposed indication is for the intravenous administration of 1 percent (10 milligrams per milliliter (mg/mL)) propofol injectable emulsion for the initiation and maintenance of minimal-to-moderate sedation in adult

patients (American Society of Anesthesiology physical status I and II) undergoing colonoscopy and esophagogastroduodenoscopy (EGD) procedures.

At a May 28, 2009 meeting, the Anesthesiology and Respiratory Therapy Devices Panel met to discuss, and provide recommendations regarding, the PMA. The panel recommended, by a vote of 8-2, that the PMA be found "approvable with conditions."

On February 26, 2010, CDRH issued a letter to EES indicating that PMA P080009 was not approvable under § 814.44(f) (21 CFR 814.44(f)) because CDRH concluded that the data and information offered in support of the PMA did not provide a reasonable assurance that the device is safe under the conditions of use prescribed, recommended, or suggested in the proposed labeling, as required by section 515(d)(2)(A) of the FD&C Act.

On March 25, 2010, EES requested review of the not approvable letter. Submitted in the form of a petition for reconsideration under 21 CFR 10.33 (see § 814.44(f)(2)), EES's petition stated that, in accordance with § 814.44(f), EES considered the not approvable letter to be a denial of approval of PMA P080009 under § 814.45 (21 CFR 814.45). In accordance with section 515(d)(4) of the FD&C Act, EES requested review of this denial under section 515(g)(2) of the FD&C Act.

Subsequently, on October 26, 2010, CDRH issued an order denying approval of the SEDASYS PMA (Denial Order), as required by § 814.45(e)(3). On November 5, 2010, in accordance with section 515(g)(2) of the FD&C Act, FDA granted EES's petition for review of the order denying PMA P080009.

In accordance with section 515(g)(2) of the FD&C Act, the Office of the Commissioner referred PMA P080009 and the basis for the order denying its approval to the Medical Devices Dispute Resolution Panel, an advisory committee of experts established, in part, to receive

referrals of petitions for advisory committee review under section 515(g)(2)(B) of the FD&C Act. (See 76 FR 15321, March 21, 2011.) The advisory committee of experts for this review consists of nine persons, qualified by training and experience to evaluate the clinical and scientific basis of CDRH's order denying approval of the PMA. After independent study of the data and information furnished to it by the Office of the Commissioner, and other data and information before it, this advisory committee will submit to the Chief Scientist and Deputy Commissioner for Science and Public Health (Chief Scientist), the Commissioner's designee and an official authorized to perform all delegable functions of the Commissioner, a report and recommendation with respect to the order, together with the underlying data and information and a statement of the reasons or basis for the recommendation. (See section 515(g)(2)(A) of the FD&C Act.)

The Office of the Commissioner will make the report and recommendation public in accordance with section 515(g)(2)(C) of the FD&C Act. The Office of the Commissioner will also provide a copy of that report and recommendation to EES and CDRH, and will offer EES and CDRH the opportunity to submit comments on the report and recommendation before a final order is rendered. In accordance with section 515(g)(2)(C) of the FD&C Act, the Chief Scientist will issue an order either affirming or reversing the order denying PMA P080009 and, if appropriate, approving or denying approval of the PMA.

II. Meeting Issues and Process

A. Issues

Two major disputed clinical and scientific issues raised in CDRH's Denial Order are as follows: (1) Whether, given CDRH's view that, as it states in that order, "the SEDASYS System is associated with an increased incidence of deeper-than-intended sedation" in the pivotal study,

the PMA provides a reasonable assurance that SEDASYS is safe for its proposed intended use by health care providers who have not been trained in the administration of general anesthesia; and (2) the adequacy and appropriateness of the control arm used by EES in the pivotal clinical trial for the device.

Regarding the first issue, CDRH's Denial Order maintained that the data provided demonstrates that "the SEDASYS System is associated with an increased incidence of deeper-than-intended sedation, including episodes of general anesthesia, compared to the 'Current Standard of Care' arm that was used as a control." CDRH asserted in that order that it considered these observations to represent a "serious safety signal" that would require restricting use of the device to persons trained in the administration of general anesthesia. EES's position is that the five patients experiencing transient episodes of general anesthesia do not represent a safety concern because none experienced any apnea or oxygen desaturation, that the device has built-in safety features designed to avoid progression to apnea or oxygen desaturation, and that SEDASYS was associated with a significant reduction in the primary safety endpoint (AUC_{Desat}), among other reasons.

CDRH's Denial Order also maintained that EES's "current proposal to mitigate the risks associated with the observed increased incidence of deeper-than-intended sedation, namely a targeted-training program, is inadequate because an outcome-based clinical study that would enable evaluation of the proposed training protocol has not been conducted." EES's petition for review of CDRH's Not Approvable determination countered that EES's proposed training program for SEDASYS "is validated by the training the pivotal study investigators received prior to the start of the study and the outcomes of the study."

With respect to the control arm used in the clinical trial, EES's pivotal study was a non-

blinded comparison of propofol administration by gastroenterology teams via SEDASYS with administration of benzodiazepine/opioid combinations by gastroenterology teams. CDRH maintains that, given the risks involved in administering propofol with SEDASYS that it believed were demonstrated in the pivotal study, the use of the device by the intended group of clinicians needs to be compared to propofol administration in a treatment arm without the device by health care professionals trained in the administration of general anesthesia, as contemplated by the drug labeling for propofol. EES's position is that the clinical trial design appropriately compares the device with the "current standard of care"--benzodiazepine/opioid combinations--that it would supplant and provides reasonable assurance of safety and effectiveness.

Questions for the advisory committee to consider relative to the safety issue are:

1. Do the incidents of deeper-than-intended sedation observed in the SEDASYS pivotal trial, including general anesthesia in five patients in the SEDASYS group compared to one patient in the control group, represent a clinically significant safety concern?
2. Do any probable benefits to health from use of SEDASYS outweigh any probable risks?
3. Was the clinical trial comparing propofol administration by gastroenterology teams via SEDASYS with administration of benzodiazepine/opioid combinations by gastroenterology teams appropriate to determine whether there is a reasonable assurance that the device is safe for its proposed intended use?
4. Should a clinical trial instead compare administration of propofol by gastroenterology teams via SEDASYS with administration of propofol without the device by persons trained in the administration of general anesthesia?
5. Does the PMA demonstrate that the training EES proposed for the intended user group

adequately addresses the risk of incidents of deeper-than-intended sedation, including the incidents of general anesthesia seen in the pivotal trial, and the possible consequences of these events?

6. Does the training program need to be validated to ensure that it adequately mitigates such risks, and, if so, how could this be done?

B. Process

Although no statute or regulation requires that separation of functions be applied to this proceeding, the Agency is observing separation of functions as a matter of policy in this matter. As the Center responsible for the action under review, CDRH will be, like EES, a party to the advisory committee meeting and will be responsible for presenting its position at that meeting.

In addition, as a corollary to its decision to observe a separation of functions, until the Commissioner issues an order either affirming or reversing the order denying approval of PMA P080009, the Office of the Commissioner will not engage in any ex parte communication (see 21 CFR 10.3(a)) with anyone participating as a party or any person outside the Agency with respect to the matter under consideration. Any written ex parte communication has been and will continue to be immediately served on the two parties and filed in the docket. Any oral ex parte communication has been and will continue to be immediately memorialized in writing, served on both parties, and filed in the docket.

At the meeting, each party will be provided 2 hours during the first portion of the meeting to present relevant information or views orally. The parties may use the allotted time as desired, consistent with an orderly meeting, and may be accompanied by additional persons, who may present relevant information or views. The parties will subsequently be allowed 15 minutes for rebuttal. During the advisory committee's open discussion, the advisory committee members

may pose questions to, or requests for clarification from, EES and/or CDRH. Thereafter, each party will be allocated 15 minutes for summation, after which advisory committee deliberation and voting will occur.

FDA welcomes the public's attendance at this advisory committee meeting and will make every effort to accommodate persons with physical disabilities or special needs. If you need special accommodations due to a disability, please contact Nancy Braier (see Contact Person) at least 7 days in advance of the meeting.

FDA is committed to the orderly conduct of its advisory committee meetings. Please visit our Web site at <http://www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/ucm111462.htm> for procedures on public conduct during advisory committee meetings.

Because this is a public meeting before an advisory committee, it is subject to our regulations concerning the policy and procedures for electronic media coverage of public agency administrative proceedings (§§ 10.200 through 10.206 (21 CFR 10.200 through 10.206)). These procedures are primarily intended to expedite media access to our public proceedings. Representatives of the electronic media may be permitted, subject to certain limitations, to videotape, film, or otherwise record our public administrative proceedings, including the testimony of witnesses in the proceedings. Accordingly, the parties and nonparty participants, and all other interested persons, are directed to § 10.200 through 10.206, for a more complete explanation of those regulations' effect on this meeting.

All documents filed or posted in this matter are available for public review under Docket No. FDA-2010-P-0176 in the Division of Dockets Management (see Registration and Presentations) between 9 a.m. and 4 p.m., Monday through Friday. Persons with access to the

Internet may obtain documents at <http://www.regulations.gov>. FDA intends to make background material, including briefing materials for the advisory committee provided by CDRH and EES, available to the public no later than 2 business days before the meeting. If FDA is unable to provide the background material prior to the meeting, the background material will be made publicly available at the location of the advisory committee meeting, and the background material will be available in the Division of Dockets Management (see Registration and Presentations) and at <http://www.regulations.gov> after the meeting.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

III. Transcripts

Please be advised that as soon as a transcript is available, it will be accessible at <http://www.regulations.gov>. It may be viewed at the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD.

Dated: November 14, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

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